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EXHIBIT A

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Applicants	:	MEYER et al.
Serial No.	:	10/569,714 (U.S. Patent Application Publication 2007-0077284)
Filing Date	:	September 21, 2006
For	:	**TRANSDERMAL FORMULATION COMPRISING AN OPIOID ANALGESIC AND AN ALOE COMPOSITION**
Examiner	:	CHEN, Catheryne
Art Unit	:	1655

745 Fifth Avenue
New York, NY 10151

DECLARATION UNDER 37 C.F.R. § 1.132

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Commissioner for Patents
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Alexandria, VA 22313-1450

I, Dr. Elisabeth Meyer of Kreuzberg 31c, D-83714 Miesbach, a citizen of Germany, hereby declare:

- that I am a biologist having studied at the University of Ulm (Diploma 1992);
- that I received the degree of Doctor of Natural Sciences (Dr. rer nat) in Biology at the University of Ulm in 1995;
- that I entered the employ of Acino AG, Miesbach, DE in 2002, where I am still employed and currently hold the position of Patent Affairs Manager;
- that I am currently listed as an inventor on approx. 10 U.S. patent application publications according to the USPTO database;
- that I am listed as an author on 10 peer reviewed publications;
- that I have specialized for more than 6 years in the field of skin care formulations and active ingredients.

I am an inventor in this application and have reviewed the application and final rejection of 27 October 2008.

When considering the applicants invention as a whole, the present invention provides a solution for the problem of imparting a pharmaceutical formulation with properties which enable an opiod analgesic to be transdermally administered. The solution for this problem consists in

- a transdermal formulation comprising
- a synthetic rubber adhesive selected from a styrene-butadiene-styrene block copolymer or a styrene-butadiene block copolymer,
- an opioid analgesic from the phenanthrene group or a pharmaceutically acceptable salt thereof as active ingredient and
- an aloe composition as transdermal penetration agent.

With respect to amended claim 1, the formulation comprises a synthetic rubber adhesive selected from a styrene-butadiene-styrene block copolymer or a styrene-butadiene block copolymer.

I have carried out comparative experiments which are similar to Example 1 in the specification and which are now presented for the first time with this submission this Declaration.

In Example 1 of the description of the present application experiments with different matrix patches are presented. The results are summarized in Table I on page 16 of the description. A matrix patch is provided which comprises a mixture of buprenorphine (the analgesic), an aloe (the transdermal penetration agent) and a styrene-butadiene-styrene polymer (the adhesive). Flux experiments with hairless mouse skin reveal buprenorphine fluxes in the range from 0.8 to 2.3 $\mu g/cm^2*h$ and the transdermal penetration effect of aloe compositions.

In the comparative experiments the styrene-butadiene-styrene polymer (the adhesive) was replaced by several acrylate adhesives, i.e. the adhesive which is disclosed by Fischer as the usual adhesive in combination with the intradermal penetration agent (the aloe composition) and the drug.

The results as disclosed in the description and the results of the comparative experiments are presented in the following table below (see next page):

Adhesive type	PSA	Buprenorphine (% w/w)	*Aloe vera* (% w/w)	Flux (hairless mouse skin)	Formation of crystals
Examples of the Present Invention (cf. Table I of the invention, page 16)					
Styrene-butadiene-styrene polymer	DT 6173	15	20	2.3 µg/(cm^2*h)	–
Styrene-butadiene-styrene polymer	DT 6173	5	20	0.8 µg/(cm^2*h)	–
Styrene-butadiene-styrene polymer	DT 6173	10	10	0.9 µg/(cm^2*h)	–
Comparative Examples					
Acrylate-vinylacetate with carboxy groups	DT 2825	10	10	1.1 µg/(cm^2*h)	+
Acrylate-vinylacetate with hydroxyl groups	DT 2287	10	10	1.1 µg/(cm^2*h)	+
Acrylate with functional hydroxy groups	DT 2510	10	10	1.3 µg/(cm^2*h)	+
Acrylate-vinylacetate without functional groups	DT 4098	10	10	1.5 µg/(cm^2*h)	+

It should first be noted that in the description of the present application the fluxes are accidentally given as g/(cm^2*h). In fact, also in the case of the invention the fluxes are in the micro gram range and should read as µg/(cm^2*h) which is corrected in the specification.

When comparing the results of the above experiments in which the patches comprise 10 % (w/w) *Aloe vera* it turns out that the fluxes which are obtained with the styrene-butadiene-styrene polymers as adhesive (according to the invention) and with the acrylates as adhesives (comparative examples) are similar. However, with the acrylate polymers a disadvantageous crystallisation of the drug (buprenorphine) in the matrix is observed over the time. Such a crystallisation reduces the long term stability of the formulations and the amount of drug available for the transdermal penetration and is very disadvantageous for transdermal applications, for which a relatively high concentration of the dissolved drug in the pharmaceutical formulation is needed. This disadvantageous crystallisation effect can be avoided using the styrene-butadiene-styrene polymers of the invention.

The Fischer invention does not comprise any hint that, different from acrylates, styrene-butadiene-styrene polymer adhesives in pharmaceutical formulations can prevent crystallisation of the drug, whereby the long term stability of formulations comprising buprenorphine and an aloe composition are improved and whereby the formulations may be used as transdermal formulations.

The undersigned hereby declares as follows:

The undersigned further declares that all statements made herein of his or her own knowledge are true and that all statements made on information and belief are believed to be true; and that the foregoing statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 26 August 2009 By: E. Meyer

Dr. Elisabeth Meyer

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EXHIBIT B

Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems

EIGHTH EDITION

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Transdermal Drug Delivery Systems

11

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Transdermal drug delivery systems (TDDSs) facilitate the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects. In 1965 Stoughton first conceived of the *percutaneous absorption* of drug substances (1). The first transdermal system, Transderm Scop (Ciba, now Novartis) was approved by the Food and Drug Administration (FDA) in 1979 for prevention of nausea and vomiting associated with travel, particularly by sea.

Evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and/or its metabolites in the urine, and clinical response of the patient to the therapy. With transdermal drug delivery, the blood concentration needed to achieve therapeutic efficacy may be determined by comparative analysis of the patient's response to drug blood levels. For transdermal drug delivery, it is considered ideal for the drug to migrate through the skin to the underlying blood supply without buildup in the dermal layers (2). This is in direct contrast to the types of topical dosage forms discussed in the previous chapter, in which drug residence in the skin, the target organ, is desired.

As discussed in the previous chapter, the skin is composed of the stratum corneum (the outer layer), the living epidermis, and the dermis, which together provide the skin's barrier layers to penetration by external agents (see Fig. 10.6). The film that covers the stratum corneum is composed of sebum and sweat, but because of its varied composition and lack of continuity, it is not a significant factor in drug penetration, nor are the hair follicles and sweat and sebaceous gland ducts, which constitute only a minor proportion of the skin's surface.

Percutaneous absorption of a drug generally results from direct penetration of the drug through the stratum corneum, a 10- to 15-μm-thick layer of flat, partially desiccated nonliving tissue (3, 4). The stratum corneum is com-

than in the gluteal area. If a series of injections are to be given, the injection site is usually varied. To be certain that a blood vessel has not been entered, the clinician may aspirate slightly on the syringe following insertion of the needle to observe any blood entering the syringe. The volume of medication that may be conveniently administered by the intramuscular route is limited, generally to a maximum of 5 mL in the gluteal region and 2 mL in the deltoid of the arm.

The Z-track technique is useful for intramuscular injections of medications that stain upper tissue, such as iron dextran injection, and those that irritate tissue, such as diazepam, by sealing these medications in the lower muscle. Because of its staining qualities, iron dextran must be injected only into the muscle mass of the upper outer quadrant of the buttock. The skin is displaced laterally prior to injection, then the needle is inserted and syringe aspirated, and the injection performed slowly and smoothly. The needle is then withdrawn and the skin released. This creates a Z pattern that blocks infiltration of medication into the subcutaneous tissue. The injection is 2 to 3 inches deep, and a 20- to 22-gauge needle is used. To reduce further any staining of upper tissue, usually one needle is used to withdraw the iron dextran from its ampul and replaced with another for the injection.

Subcutaneous Route

The subcutaneous route may be used for injection of small amounts of medication. Injection of a drug beneath the skin is usually made in the loose interstitial tissue of the outer upper arm, the anterior thigh, or the lower abdomen. The site of injection is usually rotated when injections are frequently given, as with daily insulin injections. Prior to injection, the skin at the injection site should be thoroughly cleansed. The maximum amount of medication that can be comfortably injected subcutaneously is about 1.3 mL, and amounts greater than 2 mL will most likely cause painful pressure. Syringes with up to 3-mL capacities and 24- to 26-gauge needles are used. These needles have cannula lengths of three-eighths of an inch to an inch. Most typically, subcutaneous insulin needles are 25 to 30 gauge with length of five-sixteenths to five-eighths of an inch. Upon insertion, if blood appears in the syringe, a new site should be selected.

Irritating drugs and those in thick suspension may produce induration, sloughing, or abscess and may be painful. Such preparations are not suitable for subcutaneous injection.

Intradermal Route

A number of substances may be effectively injected into the corium, the more vascular layer of the skin just beneath the epidermis. These substances include various agents for diagnostic determinations, desensitization, or immunization. The usual site for intradermal injection is the anterior forearm. A short (three-eighths of an inch) and narrow (23- to 26-gauge) needle is usually employed. The needle is inserted horizontally into the skin with the bevel facing up. The injection is made with the bevel just disappearing into the corium. Usually only about 0.1 mL may be administered in this manner.

Specialized Access

When it is necessary to administer repeated injections over time, it is prudent to employ devices that provide continued access and reduce pain associated with administration.

Several types of central venous catheters are used in institutions and on an outpatient basis for a variety of parenteral medications (e.g., cancer chemotherapy, long-term antibiotic therapy, total parenteral nutrition solutions). They can remain in place for a few days to several months. When not in use, they require heparinization to maintain patency of the catheter lumen.

The use of indwelling plastic catheters reduces the need for multiple punctures during intravenous therapy. Composed of polyvinyl chloride, Teflon, and polyethylene, these should be radiopaque to ensure that they are visible on radiographs. Usually, these must be removed within 48 hours after insertion. The choice of catheter depends on several factors, including

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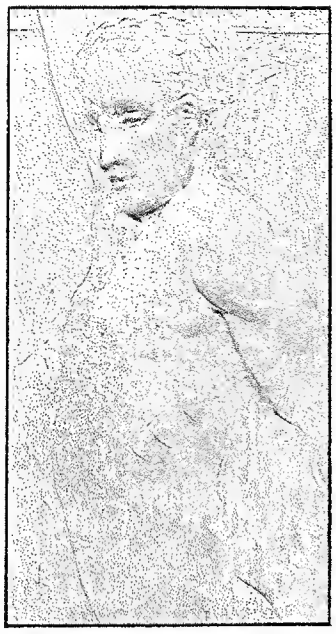
EXHIBIT C



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CLINICAL INVESTIGATION

A 27-year-old male is involved in a gasoline explosion, sustaining burns to the face, neck, chest, and arms. Upon arrival at the emergency room, he complains of intense pain in the face and neck, which exhibit extensive blistering and erythema (redness). These findings are all curiously absent on the burned chest and arms, which have a pale, waxy appearance.

Examination reveals the skin on the patient's chest and arms to be leathery in texture and without sensation, including pain. The emergency room (E.R.) physician comments to an observing medical student that third degree burns are present on the skin of these regions and that excision of the burn eschar (traumatized tissue) with subsequent skin grafting will be required.

Why is the area of second degree burn red, blistered, and painful, while the third degree burn is pale and insensate (without sensations, including pain)? Why will the chest and arms require skin grafting while the face and neck probably will not?

Hints: Think in terms of functions of the skin, and survival of the germinal cells in functioning skin. Examine carefully figures 7.1 and 7.13. ■

The Integument as an Organ

The integument (skin) is the largest organ of the body, and together with its epidermal structures (hair, glands, and nails), it constitutes the integumentary system. It has adaptive modifications in certain body areas that accommodate protective or metabolic functions. The integument is a dynamic interface between the continually changing external environment and the body's internal environment and aids in maintaining homeostasis.

Objective 1. Explain why the integument is considered an organ and a component of the integumentary system.

Objective 2. Describe some common clinical conditions of the integument that result from nutritional deficiencies or body dysfunctions.

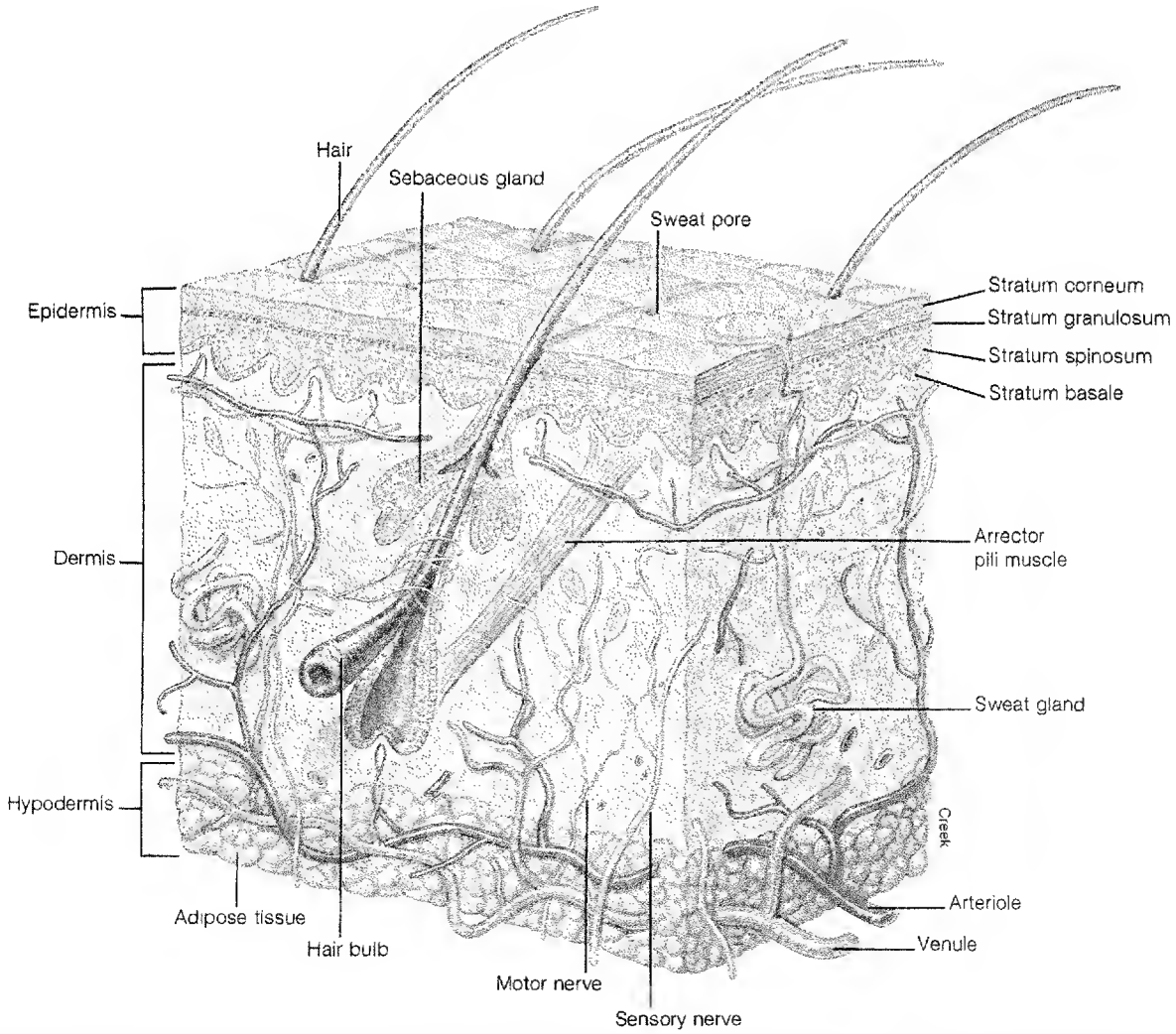

Figure 7.1 A diagram of the skin.